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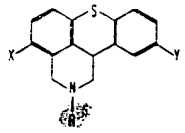
(54) TETRAHYDROPYRIDO-THIOXANTHENE DERIVATIVES, COMPOSITIONS CONTAINING THEM, AND THE PREPARATION THEREOF

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German corporate body of 61 Darmstadt, Frankfurter Strasse 250, Germany, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement: —

This invention is concerned with certain novel tetrahydropyrido-thioxanthene derivatives, their acid addition salts, compositions containing them, and processes for their preparation.

We have found that 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthenes of formula I:

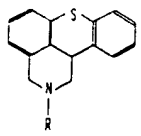


I

in which R is hydrogen or an alkyl group having 1 to 4 carbon atoms, X is hydrogen, an alkyl group having 1 to 4 carbon atoms or chlorine, and Y is hydrogen, an alkyl group having 1 to 4 carbon atoms or chlorine, and their physiologically acceptable acid addition salts, have valuable pharmacological properties. These compounds have a persistent tranquillizing and/or hypnotic and/or anti-depressant and/or narcosis-potentiating action combined with good tolerance, low toxicity and wide therapeutic range. It is an advantage of these compounds, which act on the central nervous system, that they have slight muscle-relaxant action.

The compounds of formula I and their acid addition salts are novel and constitute one aspect of the present invention.

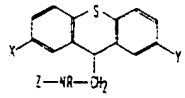
A preferred class of novel compounds are 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthenes of formula Ia:



Ia

in which R has the above-stated meaning, and their physiologically acceptable acid addition salts.

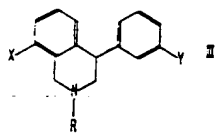
The present invention also comprises processes for the preparation of 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n] - thioxanthenes of formula I and their acid addition salts. A first process comprises cyclizing a compound of formula II:



II

in which R, X and Y have the above-stated meaning, Z is —CHO or —CH_2Q, and Q is an OH group or a reactively esterified OH group.

A second process comprises reacting a compound of formula III:



in which R, X and Y have the above-stated meanings, with sulphur dichloride, disulphur dichloride, sulphur or with a reactant which splits off sulphur under the reaction conditions whereby an intramolecular thio-ether bridge is formed.

A third process comprises reducing a compound corresponding to formula I except that it has one or more reducible groups in the nitrogen-containing ring, preferably one or more double bonds, particularly in the 2,3- and/or 1,11b- or 1,2-positions, or a carbonyl group in the 1- and/or 3-positions, and which may be in the form of a corresponding quaternary salt when it contains a double bond in the 1,2- and/or 2,3-positions.

The compound according to the invention obtained by any one of the foregoing processes may, if desired, additionally be treated with an alkylating agent and/or converted into a physiologically acceptable acid addition salt thereof by treatment with an acid or, when it is an acid addition salt, be treated to liberate a base of formula I therefrom.

When the substituents R, X and Y are alkyl groups they are preferably methyl, ethyl or n-propyl. But these substituents may also be isopropyl, n-butyl, isobutyl, secondary butyl or tertiary butyl.

The compounds of formula I have an asymmetrical carbon atom. They are therefore obtained by synthesis in the form of racemates. These racemates may be used as such, but may, if desired, be separated into their enantiomers in known manner by treatment with optically active acids, for example tartaric acid, camphorsulphonic acid, mandelic acid, malic acid, lactic acid or other compounds suitable for separating racemates. Separation of racemates may, in general, be effected by the methods described in the literature.

The compounds of formula I are preferably obtained by cyclizing compounds of formula II. The substituent Q in the compounds of formula II may be, in addition to an OH group, chlorine or bromine, or an alkylsulphonyloxy group, preferably containing 1 to 6 carbon atoms, for example methanesulphonyloxy, or an arylsulphonyloxy group, preferably containing 6 to 10 carbon atoms, for example benzenesulphonyloxy or, particularly, p-toluenesulphonyloxy.

Preferred starting compounds of formula II are those in which Z is —CHO. These may be obtained from the known 10-aminomethylthioxanthenes (according to formula II, Z=H) by formylation, for example by heating with formic acid or reacting with formic acid esters, such as formic acid methyl ester or formic acid ethyl ester. When a compound of formula II (Z=CHO) is cyclized, there is formed by disproportionation, besides the desired compound I, the same quantity of a compound of formula IVa below, which may also be converted into a compound of formula I as described below.

Starting compounds of formula II (Z=CH_2Q) are preferably produced *in situ*, by reacting the known 10-aminomethylthioxanthenes (according to formula II, Z=H) in a suitable solvent with formaldehyde or formaldehyde-yielding compounds (such as polyoxymethylene, paraformaldehyde, and formaldehyde dimethylacetal) and reactively esterifying the resulting compound of formula II (Q=OH). Hydrochloric acid, hydrobromic acid, methane sulphochloride, p-toluene sulphochloride or benzene sulphochloride may, for example, be used to effect esterification.

The compound of formula II may, in particular, be cyclized by the action of acid catalysts to form the compounds of formula I. The catalysts used are preferably mineral acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, the latter being particularly preferred where Z is a formyl group; PCl_3; PCl_5; $POCl_3$; organic sulphonic acids, such as toluenesulphonic acids or camphorsulphonic acid; Lewis acids, such as aluminium chloride, boron fluoride or zinc chloride; or acid salts, such as potassium hydrogen sulphate.

Cyclization may be carried out in the presence of an additional solvent, for example in the presence of a lower alcohol, such as methanol or ethanol; an ether, such as dioxan or tetrahydrofuran; an ester; a carboxylic acid, such as acetic acid; a hydrocarbon such as tetrahydronaphthalene, benzene or toluene; nitrobenzene; a chlorinated hydrocarbon, such as methylene chloride or chloroform; or concentrated hydrochloric acid; or, if desired, in a mixture of two or more of these solvents. An excess of the cyclizing agent may also be used as a solvent. Cyclization is suitably effected at a temperature of from 0 to 300°C; it may be accelerated by heating, where appropriate to the boiling point of the solvent used. The reaction time is from a few minutes to several days. These reaction conditions give a reaction mixture from which the compound of formula I can be isolated by chromatographic methods.

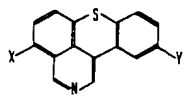
The compounds of formula I can also be obtained by introducing a thioether bridge into the compounds of formula III. The compounds of formula III can be prepared, for example, by cyclizing N-formyl-2,2-diphenyl-1-aminoethanes, substituted where

appropriate in the phenyl rings, with phosphoric acid and then reducing the resulting 3,4 - dihydro - 4 - phenylisoquinoline to form compounds of formula III (R=H); if desired, alkylation at the nitrogen atom may then be effected to give a compound of formula III (R=alkyl containing 1 to 4 carbon atoms).

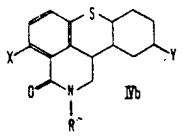
Preferred starting compounds of formula III are those in which X and Y are hydrogen.

As stated above, suitable thioether-bridge-forming reactants are sulphur dichloride, disulphur dichloride, sulphur and any reactant which splits off sulphur under the reaction conditions, such as sulphides, polysulphides or thiosulphates. It is advantageous to use catalysts of the Friedels-Crafts type, such as aluminium chloride, boron fluoride, lithium bromide or their etherates or alcoholates, but the reaction may also be carried out with other catalysts or without a catalyst.

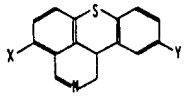
The compounds of formula I may also be obtained by reducing compounds that are the same as formula I except that they contain at least one double bond or a carbonyl group in the nitrogen-containing ring, in particular compounds of formulae IVa to IVc; compounds IVa and IVc may also be in the form of their quaternary ammonium salts IVd or IVe.



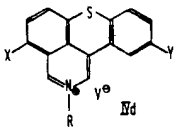
IVa



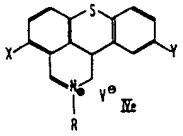
IVb



IVc



IVd

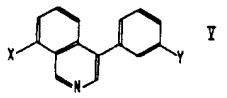


IVe

in which X, Y and R have the above-stated meanings and V is an acid radical.

The starting compounds of formula IVa may, for example, be prepared from the compounds of formula II, in which Z is a formyl group, by cyclizing these as described above. Disproportionation results in the formation of equal parts of the compounds of formulae I and IVa. The compound IVa may be separated and then reduced to form a compound of formula I, or the whole reaction mixture may be treated with a reducing agent which has the effect of reducing the compound of formula IVa without isolation to form a compound of formula I.

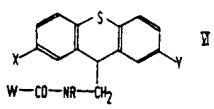
The compounds of formula IVa may also be prepared by reacting a compound of formula V



V

in which X and Y have the above-stated meanings, with a thioether-bridge-forming reactant as described above. The compounds of formula V may be in the form of their quaternary salts with the corresponding anion, as a result of alkylation at the nitrogen atom with an alkyl group of 1 to 4 carbon atoms. The reaction is carried as as described above.

The starting compounds of formula IVb can be prepared by cyclizing a compound of formula VI



VI

in which R, X and Y have the above-stated meanings and W is Cl, methoxy or ethoxy, which, in turn, may be prepared by reacting the known corresponding 10-aminoethylthioxanthenes with phosgene, chloroformic acid methyl ester or chloroformic acid ethyl ester.

The starting compounds of formula IVc can be prepared by cyclizng compounds of formula II (Z=CHO) under mild conditions.

These compounds, particularly those of formulae IVa to IVc, are preferably reduced by catalytic hydrogenation or by treatment with complex metal hydrides.

Nobel metal, nickel and cobalt catalysts and also copper chromium oxide are, for example, suitable as catalysts for hydrogenation. The noble metal, catalysts may be in the form of supported catalysts, for example palladium on carbon, calcium carbonate or strontium carbonate; oxide catalysts, for example platinum oxide; or fine-grained metal catalysts. Nickel and cobalt catalysts are advantageously used as Raney metals, and nickel also on kieselguhr or pumice as a carrier.

Hydrogenation may be carried out at room temperature and normal pressure or at an elevated temperature and/or pressure.

It is preferred to use a pressure of from 1 to 200 atm and a temperature of from −80

to +150°C. The reaction is advantageously carried out in the presence of a solvent, such as methanol, ethanol, isopropanol, ethyl acetate, dioxan, glacial acetic acid, tetrahydrofuran or water. In many cases it is advisable to add mineral acid, for example hydrochloric or sulphuric acid. The free bases, for example, IVa and IVc, their acid addition salts or the quaternary salts IVd and IVe may be used for hydrogenation. Care must, of course, be taken that the benzene rings are not also attached during hydrogenation. It is therefore preferable to stop the hydrogenation when the calculated quantity of hydrogen has been taken up.

Complex metal hydrides, particularly $LiAlH_4$ and $NaBH_4$, where appropriate with the addition of catalysts such as BF_3, $AlCl_3$ or LiBr, may also advantageously be used as reducing agents. These reductions are advantageously carried out in the presence of an inert solvent, such as ether, tetrahydrofuran, ethylene glycol dimethyl ether or pyridine; the operation may also be carried out in aqueous or alcoholic solutions if $NaBH_4$ is used. The reduction is advantageously carried out at a temperature of from −80°C to the boiling point of the solvent, in particular of from 0° and 100°C. The metal complexes formed may, for example, be decomposed with moist ether, an aqueous solution of ammonium chloride or aqueous solutions of alkali hydroxide, preferably in equivalent quantities.

Finally, the compounds of formula I may be converted by treatment with acids into their physiologically acceptable acid addition salts; acids that yield physiologically acceptable salts are used for this reaction.

Thus, organic and inorganic acids, for example, aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic or sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, oxalic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, aminocarboxylic acids, sulphamic acid, benzoic acid, salicyclic acid, phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isoniconic acid, methanesulphonic acid, ethanedisulphonic acid, naphthalene monosulphonic acid, naphthalene disulphonic acid, sulphuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, or phosphoric acids, suh as orthophosphoric acid, may be used.

For use in human or veterinary medicine, the novel compounds are used in admixture with solid and/or liquid and/or semi-liquid excipients. Suitable excipients or carriers are organic or inorganic substances that are suitable for parenteral, enteral or topical application and do not react with the novel compounds, for example water, vegetable oils, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talcum, petroleum jelly, and cholesterol. For parenteral application there are used, in particular, solutions, preferably oily or aqueous solutions, and suspensions, emulsions or implants. For enteral application, tablets, dragees, syrups and liquors are suitable, and for topical application, ointments, creams and powders. The preparations indicated may be sterilized and/or may additionally contain adjuvants, such as preserving, stabilizing or wetting agents, salts to influence the osmotic pressure, buffer substances, or colouring, flavouring and/or perfuming substances.

When the novel compounds according to the invention are formulated in dosage unit form, the latter preferably contain from 1 to 500 mg of the compound per dosage unit.

In order that the invention may be more fully understood, the following examples, in which all temperatures are in °C, are given by way of illustration only:—

Example 1

a) 120 g of 10-formylaminomethylthioxanthene (m.p. 130—131°; obtainable by boiling 10-aminomethylthioxanthene for 12 hours with formic acid in toluene) were added to a mixture of 524 g of phosphorus pentoxide and 404 g of 89% phosphoric acid which had previously been stirred for 4 hours at 140°. The whole was heated to 200° over a period of 30 minutes with stirring, this temperature was maintained for 2 hours, and the mixture was then cooled to 100°. After the addition, drop by drop, of 560 ml. of water and 1850 ml of 47% aqueous caustic potash solution, the whole was left to cool to room temperature and then extracted with chloroform. The chloroform solution (A) was dried and evaporated. 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene was isolated from the reaction product by column chromatography and was precipitated with ethanolic hydrobromic acid in the form of the hydrobromide. Extraction by boiling with ethanol, suction filtration, and drying yielded 1,2,3, 11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 305°. Pyrido [3,4,5 : m,n]-thioxanthene, m.p. 146°, was also recovered from the reaction mixture.

From:

2 - chloro - 10 - formylaminomethylthioxanthene (m.p. 126°)

2 - methyl - 10 - formylaminomethyl - thioxanthene

2,8 - dichloro - 10 - formylaminomethyl - thioxanthene

2,8 - dimethyl - 10 - formylaminomethyl - thioxanthene

the following may be obtained by treatment with polyphosphoric acid:

4 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene (m.p. 109—110°; hydrobromide, m.p. 309—310°),

10 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene (hydrobromide m.p. 306°; methanesulphonate, m.p. 229°),

4 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4,10 - dichloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene,

4,10 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene,

the following being obtained as by-products respectively;

4-chloropyrido [3,4,5 : m,n]-thioxanthene

10 - chloropyrido [3,4,5 : m,n] - thiox - anthene

4-methylpyrido [3,4,5 : m,n]-thioxanthene

10 - methylpyrido [3,4,5 : m,n] - thiox - anthene

4,10 - dichloropyrido [3,4,5 : m,n] - thiox - anthene

4,10-dimethylpyrido [3,4,5 : m,n]-thiox-anthene.

2 - Chloro - 10 - formylaminomethyl - thioxanthene (m.p. 126°) can be prepared by a reaction of 5-chloro-2-mercaptobenzoic acid, benzene and sulphuric acid to form 2-chlorothioxanthone (m.p. 153—154°), reduction of the latter with phosphorus/hydrogen iodide to form 2-chlorothioxanthene (m.p. 99—100°), stepwise treatment with lithium butyl, carbon dioxide (2-chlorothioxanthene-10-carboxylic acid, m.p. 200°), thionyl chloride, ammonia (2-chlorothioxanthene-10-carboxylic acid amide, m.p. 184°), lithium aluminium hydride/aluminium chloride, hydrobromic acid (2-chloro-10-aminomethyl-thioxanthene hydrobromide, m.p. 276—277°) and boiling with formic acid in toluene.

2 - Methyl - 10 - formylaminomethyl - thioxanthene can be obtained similarly using 5-methyl-2-mercaptobenzoic acid as starting material.

b) 5 g of 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene, 30 ml of formic acid, 1.1 g of sodium formate and 4.3 ml of 35% aqueous formaldehyde solution were mixed, heated to 60° for 3 hours and then boiled overnight. The reaction mixture was then evaporated, the residue was taken up in dilute hydrochloric acid, and the solution was washed with ether. The acid aqueous phase was made alkaline and extracted with ether. After the addition of ethanolic hydrobromic acid, suction filtration and drying, 2-methyl-1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 241—242°, was obtained. 2 - Methyl - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n] - thioxanthene methanesulphonate, m.p. 218°, may be obtained similarly by precipitation with ethanolic methanesulphonic acid.

From:

4 - Chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4,10 - dichloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene, and

4,10 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene,

there may be obtained similarly:

2 - methyl - 4 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene, methanesulphonate, m.p. 197—198°,

2 - methyl - 10 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene, methanesulphonate, m.p. 194—195°,

2,4 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene,

2,10 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene,

2 - methyl - 4,10 - dichloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene, and

2,4,10 - trimethyl - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene, and their salts.

c) 8.8 g of 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene was dissolved in 30 ml of acetonitrile and 2 g of ethyl bromide was added. After the whole had stood overnight, ether was added, whereupon unreacted starting material was precipitated in the form of the hydrobromide and was removed by suction filtration. The filtrate was evaporated, the residue was dissolved in ether, and ethanolic hydrobromic acid was added. The hydrobromide that precipitated was recrystallized from ethanol/ether. 2-Ethyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene hydrobromide, m.p. 236°, was obtained.

The following may be prepared similarly using n-propyl- and isobutyl bromide, respectively, in place of ethyl bromide:

2 - n - Propyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 216°;

2 - isobutyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 234°.

EXAMPLE 2

a) 53 g of pyrido [3,4,5 : m,n]-thioxanthene, m.p. 146°, obtained as a by-product in accordance with Example 1a, were added to a mixture of 10 g of lithium aluminium hydride and 67 g of anhydrous aluminium chloride in 800 ml of absolute ether and boiled for 15 hours. A solution of 71 g

of sodium hydroxide in 200 ml of water was then added cautiously drop by drop, the aluminium hydroxide granulate was removed by suction filtration, the remaining reaction mixture was washed with ether, and the hydrobromide was precipitated from the ether solution by the addition of ethanolic hydrobromic acid. 1,2,3,11b - Tetrahydro - pyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 305° was obtained.

From:

4-chloropyrido [3,4,5 : m,n]-thioxanthene,

10 - chloropyrido [3,4,5 : m,n] - thiox - anthene,

4-methylpyrido [3,4,5 : m,n]-thioxanthene,

10 - methylpyrido [3,4,5 : m,n] - thioxanthene,

4,10 - dichloropyrido [3,4,5 : m,n] - thiox - anthene, and

4,10-dimethylpyrido [3,4,5 : m,n]-thioxanthene

there may be prepared by similar treatment:

4 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4,10 - dichloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene, and

4,10 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

b) The chloroform extract (A) obtained as in Example 1a was evaporated, the residue was added without chromatographic separation to a mixture of 15 g of lithium aluminium hydride and 100 g of anhydrous aluminium chloride in 1.5 l of absolute ether, and the whole was boiled for 17 hours. 106 g of sodium hydroxide in 300 ml of water were added drop by drop with ice cooling. The aluminium hydroxide granulate was removed by suction filtration, the remaining reaction mixture was washed with ether, and the hydrobromide was precipitated with alcoholic hydrobromic acid. 1,2,3,11b-Tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 305°, was obtained.

The following may be prepared similarly from the other starting compounds mentioned in Example 1a:

4 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene (hydrobromide m.p. 309—310°),

10 - Chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

10 - methyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene,

4,10 - dichloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene, and

4,10 - dimethyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

Example 3

22.3 g of 2-methyl-4-phenyltetrahydroisoquinoline hydrobromide (m.p. 222°, obtainable by cyclization of N-formyl-2,2-diphenyl-1-aminoethane with polyphosphoric acid, hydrogenation on Raney nickel and methylation with formaldehyde/formic acid), 12 g of sulphur dichloride and 16 g of anhydrous aluminium chloride were stirred in 500 ml of carbon disulphide for 12 hours at 30°. The whole was then poured on to ice and hydrochloric acid, the organic phase was separated, and tartaric acid was added to the acid aqueous phase. The addition of dilute caustic soda solution was followed by extraction with ether and drying over sodium sulphate, and 2-methyl-1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene methanesulphonate, m.p. 182°, was precipitated with methanesulphonic acid.

Example 4

a) 23.5 g of pyrido [3,4,5 : m,n]-thioxanthene prepared as a by-product according to Example 1a were shaken with 100 ml of methanol and 5 g of Raney nickel in an autoclave at 120° and 180 atm hydrogen pressure. After 0.2 mol of hydrogen had been taken up, the catalyst was removed by suction filtration, and 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 305°, was precipitated by the addition of ethereal hydrochloric acid.

b) 5 ml of methyl iodide were added to 11.6 g of pyrido [3,4,5 : m,n]-thioxanthene in nitromethane and the whole was stirred for 15 hours at 35°. The reaction mixture was evaporated, the residue was taken up in and then precipitated from ethanol/water, and was then dried. Pyrido [3,4,5 : m,n]-thioxanthene-2-methoiodide, m.p. 243—245°, was obtained; this was dissolved in 50 ml of methanol and hydrogenated in an autoclave in the presence of 3 g of Raney nickel at 50° and 50 atm hydrogen pressure. When the hydrogen pressure ceased to fall, the reaction mixture was filtered with suction aod the product precipitated with ethereal hydrobromic acid.

After dissolving and precipitating from methanol/ether and then drying, 2-methyl-1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene hydrobromide, m.p. 241—242°, was obtained.

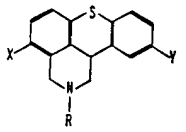
Example 5

Using the conditions and procedure of Example 1c 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene can be reacted with isopropyl bromide (or n-butyl bromide, respec-

tively) to yield 2-isopropyl-1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene (or 2-n - butyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene, respectively).

WHAT WE CLAIM IS:—

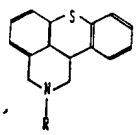
1. A 1,2,3,11b-tetrahydropyrido [3,4,5 : m,n]-thioxanthene of the formula:



I

in which R is hydrogen or an alkyl group having 1 to 4 carbon atoms, X is hydrogen, an alkyl group having 1 to 4 carbon atoms, or chlorine, and Y is hydrogen, an alkyl group having 1 to 4 carbon atoms, or chlorine, or an acid addition salt thereof.

2. A 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene of the formula:



Ia

in which R is hydrogen or an alkyl group having 1 to 4 carbon atoms, or an acid addition salt thereof.

3. 1,2,3,11b - Tetrahydropyrido [3,4,5 : m,n]-thioxanthene.

4. 2 - Methyl - 1,2,3,11b - tetrahydro - [3,4,5 : m,n]-thioxanthene.

5. 2 - Ethyl - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene.

6. 2 - n - Propyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

7. 2 - Isopropyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

8. 2 - n - Butyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

9. 2 - Isobutyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

10. 4 - Chloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

11. 2 - Methyl - 4 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene.

12. 4 - Methyl - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

13. 2,4 - Dimethyl - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene.

14. 10 - Chloro - 1,2,3,11b - tetrahydro - pyrido [3,4,5 : m,n]-thioxanthene.

15. 2 - Methyl - 10 - chloro - 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]-thioxanthene.

16. 10 - Methyl - 1,2,3,11b - tetrahydro - pyrido [3,4.5 : m,n]-thioxanthene.

17. 2,10 - Dimethyl - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene.

18. 4,10 - Dichloro - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene.

19. 2 - Methyl - 4,10 - dichloro - 1,2,3, 11b - tetrahydropyrido [3,4,5 : m,n] - thiox - anthene.

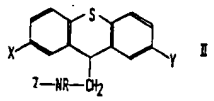
20. 4,10 - Dimethyl - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene.

21. 2,4,10 - Trimethyl- - 1,2,3,11b - tetra - hydropyrido [3,4,5 : m,n]-thioxanthene.

22. A pharmaceutical composition comprising a compound as claimed in any of of claims 1 to 21 and an inert, physiologically acceptable carrier.

23. A pharmaceutical composition according to claim 22 in dosage unit form, each dosage unit containing from 1 to 500 mg of said compound.

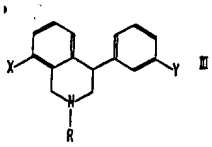
24. A process for the preparation of a 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene of formula I specified in claim 1, which comprises cyclizing a compound of formula II



II

in which A, X and Y have the meanings specified in claim 1, Z is —CHO or $—CH_2Q$, and Q is an OH group or a reactively esterified OH group.

25. A process for the preparation of a 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene of formula I specified in claim 1, which comprises reacting a compound of formula III



III

in which R, X and Y have the meanings specified in claim 1, with sulphur dichloride, disulphur dichloride, sulphur or with a reactant which splits of sulphur under the reaction conditions whereby an intramolecular thio-ether bridge is formed.

26. A process for the preparation of a 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n] - thioxanthene of formula I specified in claim 1, which comprises reducing a compound corresponding to said formula I except that it has one or more reducible groups in the nitrogen-containing ring.

27. A process according to claim 26, in which the starting compound has one or more double bonds in the 1,3- and/or 1,11b-

or 1,2-positions or a carbonyl group in the 1- and/or 3-positions.

28. A process according to claim 26, in which the starting compound has a double bond in the 1,2- or 2,3-position and is in the form of a quaternary salt.

29. A process according to any of claims 24 to 28, in which the product obtained is additionally treated with an alkylating agent and/or converted into a physiologically acceptable acid addition salt, or when it is an acid addition salt, is treated to liberate a base of formula I therefrom.

30. A process for the preparation of a 1,2,3,11b - tetrahydropyrido [3,4,5 : m,n]- thioxanthene of formula I specified in claim 1 or an acid addition salt thereof substantially as herein described in any of the Examples.

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